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| 09/242,202 | 11/01/1999 | EDWARD L. NELSON | 2026-4236US1 | 9749 |

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| EXAMINER | |
|---|---|
| LI, QIAN JANICE | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/242,202 | NELSON ET AL. | |
| | Examiner | Art Unit | |
| | Q. Janice Li | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-33,36-44 and 60-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,36-44 and 60-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment, supplemental amendments, response, and Declarations of Nelson and Manning filed on May 2, 2003, December 29, 2003, and April 16, 2004 have been entered. Claims 1, 6, 12, 15-23, 25, 28, 30, 36, 38, 42, 44, 63 have been amended; Claims 34, 35, and 45-59 have been canceled. Claims 66-110 are newly submitted. Currently, claims 1-33, 36-44, and 60-110 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 5/2/03 response would be addressed to the extent that they apply to current rejection.

### *Oath/Declaration*

The previous objection is withdrawn since the address of residency is given in the Oath.

### *Claim Objections*

Claims are objected to because a comma should be inserted before every "wherein" phrase.

Claim 28 is objected to because it recites "a composition comprising a composition".

Claims 41-43 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

Claims 64 are 109 are objected to because the sequence recited should be identified by a sequence ID number rather than by the figure number.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-33, 36-45, and 60-65 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is withdrawn in view of the Declaration, and datasheet from New England BioLab.

Claims 1-33, 36-44 and 60-65 stand rejected and claims 66-110 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating a specific immune response to a tumor antigen using a polynucleotide vector pITL expressing the same type of the tumor antigen under the regulatory control of human RANTES promoter and 3' splice and poly-A from human

growth hormone, and administered as disclosed in the Declaration of *Nelson* (to be detailed), does not reasonably provide enablement for stimulating a specific immune response using *any* humanized polynucleotide vector comprising *any* human derived promoter or *mammalian homolog thereof*, *any* human-derived 3' splice sequence, and *any* human derived poly A sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the response, Applicants first argue that claims 1-33, 44, and 60-64 are product but not method claims, the Office has not established that these claims are not enabled. In response, as indicated previously, since the claims recite a pharmaceutical composition, they were evaluated by that standard. Even though claims have now amended to recite "a composition for inducing an immune response" or simply recite "a humanized polynucleotide vector", in light of the specification and implications of the term "humanized", the only utility for the broadly claimed humanized vector is for use in immunotherapy in humans, i.e. as a vaccine carrier. Accordingly, with respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. Further, claim 16 clearly requires "wherein said vector induces an immune response to

said antigen". Since the vector is a composition for therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the vector is administered, therefore, will be evaluated by the standard. Further, claim 16 clearly requires that "said vector induces an immune response to said antigen", therefore, the claims will be evaluated by that standard. It is emphasized here that the not only an immune response should be induced but also that such immune response will bring about a therapeutic effect because the intended use is a therapeutic one.

Applicants then argue that it is well known in the art that challenging with an antigen would induce an immune response, thus claims are enabled. The argument is not impressive because the claimed invention is evaluated by the standard of a protective immune response, i.e. achieving the effect of vaccination or treatment of a disease. Even though administering an antigen to a subject may induce an immune response, it is still not routine in the art that a protective immune response can be induced. *Moingeon et al* (Trends Immunol 2002 Apr;23:173-5) teach at a post-filing date, "THE DISCOVERY OF NEW ANTIGENS ABLE TO ELICIT PROTECTIVE IMMUNE RESPONSES AGAINST INFECTIOUS PATHOGENS REMAINS ONE OF THE MOST IMPORTANT CHALLENGES IN VACCINOLOGY" (page 173, left column). "THE NEED FOR ANTIGEN-PRESENTATION PLATFORMS AND/OR ANTIGEN FORMULATIONS ELICITING POTENT T-CELL RESPONSES AND MUCOSAL IMMUNITY IN HUMANS, AS WELL AS THE POOR PREDICTIVE VALUE OF ANIMAL MODELS, WERE EMPHASIZED ALSO". (paragraph bridging pages 174 and 175). *Bodey et al* (Anticancer Res 2000;20:2665-76) review cancer vaccines in cancer immunotherapy, "THE THEORETICAL BASIS FOR ALL OF THESE APPROACHES IS VERY WELL FOUNDED. ANIMAL MODELS, ALBEIT HIGHLY ARTIFICIAL, HAVE YIELDED PROMISING RESULTS. CLINICAL TRIALS IN HUMANS, HOWEVER, HAVE BEEN SOMEWHAT

DISAPPOINTING...", "THE CANCER VACCINE APPROACH TO THERAPY IS BASED ON THE NOTION THAT THE IMMUNE SYSTEM COULD POSSIBLY MOUNT A REJECTION STRENGTH RESPONSE AGAINST THE NEOPLASTICALLY TRANSFORMED CELL CONGLOMERATE. HOWEVER, DUE TO THE LOW IMMUNOGENICITY OF TUMOR ASSOCIATED ANTIGENS, DOWNREGULATION OF MHC MOLECULES, THE LACK OF ADEQUATE COSTIMULATORY MOLECULE EXPRESSION, SECRETION OF IMMUNE INHIBITORY CYTOKINES, ETC., SUCH EXPECTATION ARE RARELY FULFILLED...FAULTY ANTIGEN PRESENTATION WHICH COULD RESULT IN TOLERANCE INDUCTION TO THE ANTIGENS CONTAINED WITHIN THE VACCINE, AND SUBSEQUENT RAPID TUMOR PROGRESSION." (page 2665, column one). These cited teachings establish that at the time of the instant filing date, the state of the art for DNA vaccination is far from routine, thus, specific not general guidance is required for the claimed invention.

In view of the guidance provided by the specification, the only vector that illustrated a protective effect is a humanized vector pITL expressing a tumor antigen disclosed in a later submitted Declaration. Although the specification lays out plans for testing effects of a pITL-HER2/neo vector in animal models and human clinical trials, they do not appear to be executed at the time of the filing. The declaration of *Nelson et al* submitted after the filing date illustrated a short term protective effect in a mouse tumor model via administering of pITL expressing a tumor antigen, however, the declaration is unclear with respect to how the vector is being delivered, i.e. the route of administration. In light of the state of the art, the route of administration is one of the critical elements for inducing an effective immune response. *McCluskie et al* (Mol Med 1999 May;5:287-300) teach "ROUTES OF ADMINISTRATION OF PLASMID DNA VACCINES INFLUENCES THE STRENGTH AND NATURE OF IMMUNE RESPONSES IN MICE AND NON-HUMAN

PRIMATES." (See abstract) *Torres et al* (J Immunol 1997;158:4529-32) teach "TRANSFECTED CELLS IN GENE GUN-BOMBARDED SKIN, BUT NOT NEEDLE-INJECTED MUSCLE, PLAY A CENTRAL ROLE IN DNA-INITIATED AB AND CTL RESPONSE" (abstract). *Nakano et al* (J Virol 1997;71:7101-09) teach that immune reactivity with plasmid DNA encoding HCV-E2 antigenic domains is linked to the injection mode, "DIFFERENT ROUTES OF INJECTION OF HCV E2 PLASMID CAN RESULT IN QUANTITATIVELY AND QUALITATIVELY DIFFERENT HUMORAL IMMUNE RESPONSES" (see abstract). The specification fails to teach otherwise, and the claims should be scoped to the best mode of operation.

Moreover, the specification is silent with regard to effects of any other humanized vectors comprising different combinations of promoter/enhancer/3'-splice and poly-A sequence and different antigens expressed, and how they function in stimulating an immune response. Again, the issue here is not whether one can put all elements together in a genetic construct, but whether the end product would have the capability of eliciting an appropriate protective immune response. For example, concerning the types of antigens, the claims contemplated bacteria and parasite antigens, however, it is well known in the art that the capability of antigens for inducing a protective immune response differs. Taking DNA vaccines for bacterial infections, *Strugnell et al* (Immunl Cell Biol 1997;75:364-69) review "DNA VACCINES AGAINST BACTERIAL INFECTIONS ARE UNDER REPRESENTED IN THE DNA VACCINE LITERATURE. THIS COULD REFLECT EITHER POOR RESULTS USING THIS TECHNOLOGY IN THE CONTEXT OF BACTERIAL INFECTIONS", "THE USE OF DNA VACCINES IN BACTERIAL INFECTIONS MAY BE COMPLICATED BY FUNDAMENTAL DIFFENCES BETWEEN PROKARYOTIC AND EUKARYOTIC GENES AND GENE PRODUCTS, INCLUDING MRNA STABILITY, CODON BIAS, SECONDARY STRUCTURES SURROUNDING NATIVE START SEQUENCES AND GLYCOSYLATION."

(abstract) "THE MAGNITUDE OF THE RESPONSE OBSERVED FOLLOWING VACCINATION WITH BACTERIAL ANTIGEN GENES ARE CONSISTENTLY MUCH LESS THAN THOSE ELICITED BY VIRAL DNA VACCINES. THE CHALLENGE TO SCIENTISTS INTERESTED IN PURSUING THIS EXCITING TECHNOLOGY IN THE CONTEXT OF BACTERIAL VACCINES WILL BE TO ADDRESS THIS RELATIVELY POOR IMMUNOGENICITY." (page 368, "potential problem section). The specification fails to teach how to overcome the art known hurdles, and thus it is highly unpredictable whether the claimed vector would induce an protective immune response for bacterial infections.

With respect to different combination of vector elements, the skilled in the art teaches that it is highly unpredictable how each recited element would unction in a certain cell. For example, the 3' splice sequences are modulators of the gene expression, their function as to either up- or down-regulating gene expression varies from cell to cell, and from gene to gene. Promoters suitable for human gene therapy have been the focus for developing a target gene-specific delivery system, but their function remains largely uncertain. *Nettelbeck et al* (Gene Ther 2000 April; 16:174-181) teach "SOME OF THE RECENTLY DESCRIBED EXPERIMENTAL GENE THERAPY PROTOCOLS DO INDEED MAKE USE OF NATURAL TISSUE-SPECIFIC PROMOTERS, BUT IN MANY INSTANCES THESE PROMOTERS SUFFER FROM A LACK OF ACTIVITY, SPECIFICITY OR BOTH." (the paragraph bridging page 174-175). "FREQUENTLY, HOWEVER, TISSUE-SPECIFIC OR OTHER SELECTIVE PROMOTERS ARE INEFFICIENT ACTIVATORS OF TRANSCRIPTION, WHICH SEVERELY LIMITS THEIR APPLICABILITY." *Miller and Whelan et al* (Human Gene Ther 1997 May; 8:803-815) teach " SOME CELLULAR PROMOTERS LARGELY RETAIN THE DESIRED SPECIFICITY WHEN PLACED IN VIRAL VECTORS;...NEVERTHELESS, IT IS NOT UNCOMMON THAT CELLULAR CIS-ACTING SEQUENCES LOSE SOME OR ALL OF THEIR ABILITY TO RESTRICT EXPRESSION APPROPRIATELY WHEN PLACED IN THE

CONTEXT OF A VIRAL VECTOR." "THE CELLULAR ENVIRONMENT MAY HAVE A STRONG EFFECT ON PROMOTER ACTIVITY". Base on these teachings, it would be highly unpredictable to search and identify a known or unknown human-derived promoter, 3' splice sequence, and a poly A to determine if they would function properly together in a particular vector. *Verma* also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "SEARCH FOR SUCH [USEFUL] COMBINATIONS IS A CASE OF TRIAL AND ERROR FOR A GIVEN CELL TYPE" (page 240, sentence bridging columns 2 and 3). Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for a specific combination of promoters, introns, and regulatory sequence in a particular carrier which would suitable for gene therapy. Although the instant specification provides a few preferred embodiments of the recited vectors, it is not enabled for its full scope because the specification fails to provide an adequate description of the vector elements and an enabling disclosure for the functional effects of the combination of these elements.

With respect to the mammalian homologs of any human promoter, the specification fails to teach any mammalian homolog of any human derived promoter, particularly whether they would function properly in humans. Taking the RANTES promoter as an example, the specification fails to teach which mammalian species has the homolog equivalent to human RANTES promoter, their sequence structures, and how they would function in human cells, thus, fails to provide an enabling disclosure to support the full scope of the claims.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for eliciting a protective immune response at therapeutic levels, in particular for the treatment of any and all infectious and malignant diseases, the lack of guidance provided by the specification as well as the absence of guidance for all possible combination of vector components with regard to their function in gene therapy broadly and genetic vaccination particularly, and the breadth of the claims directed to the use of numerous therapeutic gene/antigen/promoter/enhancer/3' splice and poly-A combinations via any route of administration, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

It is noted that claims 14, 66, and 76 recite at least one product with a designated ATCC number. Thus the following rule applies.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit ( see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33, 36-44, 60-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of claim recitation, "human derived promoter". It is unclear what the phrase encompasses or excludes, thus the metes and bounds of the claims are uncertain. For example, it encompasses any promoter obtained from a human, and modified by any means.

These claims are vague and indefinite because of claim recitation, "mammalian homolog". It is unclear what the term encompasses and excludes, thus the metes and bounds of the claims are uncertain.

Claims are vague and indefinite because of the claim recitation, "an antibiotic resistance encoding nucleic acid sequence". It is unclear how an antibiotic resistance could encode nucleic acid sequence.

Claim 16 is vague and indefinite because it is unclear the phrase "comprising..." on line 3 defines the antigenic epitope or the composition, thus, the metes and bounds of the claims are uncertain.

Claim 19 recites the limitation, "the tumor antigen" on line 2. There is insufficient antecedent basis for the limitation in the claim.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 7, 10, 15-19, 23-31, 36-37, 41-44, and 65 stand rejected under 35 U.S.C. 102(e) as being anticipated by *Roop et al* (US 6,143,727).

Applicants first argue that Roop et al teaches vector selection via antibiotic resistance, this is not persuasive because applicants fail to particularly point out where in the Roop patent such has been taught.

Applicants also argue that Roop et al does not discuss the importance of minimizing vector-derived polypeptides. The argument has been fully considered but found not persuasive because the cited section where Roop et al teach an expression cassette indicated that the vector lacks vector-derived polypetides, thus meet claim limitation regardless the reasons for doing so was elaborated or not.

It is noted that claim recitation "which directionally accepts cDNA" has not given patentable weight in determining the novelty of the invention. This is because it describes the intrinsic property of the sequence acceptance site, and as long as the vector comprises a cloning site as defined in the specification, the claim limitation is met. Further, the phrase "cDNA derived from rtPCR cloning via unique sites within an interrupted palindrome recognition sequence for a restriction endonucleases" has been interpreted as any cDNA, because it is a product-by-process type of phrase wherein the product is determined by the chemical composition of the product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Thus, for reasons of record and set forth above, *Roop et al* anticipate the instant claims.

Prior rejection of claims 1-3, 7-9, 15, 27, 29, and 30 under 35 U.S.C. 102(e) as being anticipated by *Carrano et al* (US 6,197,755) is withdrawn because the vector used by Carrano et al comprises antibiotic resistance gene.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 15-31, 36, 37, 41-44, 60-62, 65-71, 77-92, 96-107, 110 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755), in view of *Nelson et al* (J Immunol 1993;151:2601-12, IDS), *Nelson et al* (J Immunol 1996;157:1139-48, IDS), and *Eastman et al* (US 6,103,470), and evidenced by Promega Datasheet for pGL-2, and *Eggertsson et al* (IDS).

*Carrano et al* teach a polynucleotide vector, lacking vector derived polypeptide-coding sequence (e.g. fig. 1), comprising a promoter that may be derived from human (column 6, lines 37-39), a PCR sequence acceptance site (Example 41), such as Bgl1 (column 41, line 60), a colE1 origin (column 34, line 62-63), and an antibiotic selection sequence (figs 1 & 4a). *Carrano et al* further teach that the cloning site is inserted with a sequence that encodes a viral antigen (claim 12), and an oncogene (claim 15), for example, and further encodes a cytokine (column 7, lines 1-11). *Carrano et al* go on to teach a method of generating an immune response in a individual comprising introducing the vector by intramuscular injection (myocytes, claims 1, 2), and by skin route (APCs, because professional antigen presenting cells are present in the dermal sites, claim 8), and the administering of the recited expression vector encoding a tumor gene would generate a tumor specific cytotoxic lymphocytes. *Carrano et al* also teach administering a genetic vaccine facilitator agent, such as liposome and urea (column 2, lines 2-10). The teaching of *Carrano et al* differs from instantly claimed invention in that it does not use a RANTES promoter or lacks antibiotic resistance gene.

*Nelson et al* supplemented the teaching of *Carrano et al* by disclosing a human RANTES promoter or truncated forms thereof, e.g at 411 base pairs operably linked to a

sequence acceptance site (right column, page 2602), which directionally accepts cDNA, in a polynucleotide vector (pGL2 basic, comprising f1 origin, poly-A, sequence acceptance site, and $Amp^r$, see Promega data sheet), wherein the vector lacks nucleic acid sequences encoding vector-derived polypeptides. *Nelson et al* teach the importance of chemokine RANTES in immune response, particularly in suppressing viral replication such as HIV. *Nelson* (1996) further teaches that novel regulatory region critical for RANTES expression is found in the promoter region of RANTEs, which is useful for regulating RANTES expression as well as T lymphocytes activation. The teachings of Nelson et al provide the feasibility as well as motivation for using RANTES promoter in immune regulation. *Nelson* vector differs from the instantly claimed vector in that it comprises an antibiotic resistance-coding nucleic acid sequence.

*Eastman et al* supplemented the teachings of *Carrano et al* and *Nelson et al* by teaching that gene delivery vectors containing antibiotic resistance gene would pose a problem to humans as the resistance is imparted, and transmission of the gene to potential pathogens may be of a problem (paragraph bridging columns 2 & 3), thus, they offered other means of vector selection (abstract, claims 10 and 11), which include using suppressor tRNA (column 2, lines 18-29) or a small selectable element in the plasmid, which reduces or eliminates potential concerns about antibiotic resistant genes cloned on plasmid, but retains the advantages offered by antibiotics (column 3, lines 11-29, wherein the suppressor tRNA encompasses the elements as recited in the instant claims 62 and 107 (as evidenced by *Eggertsson et al*, e.g. table 2). *Eastman et al* also teach that all the elements in their plasmid could be easily removed or replaced as

needed when used either in human gene therapy or protein production in bacteria (e.g. paragraph bridging columns 2-3). These teachings demonstrated the state of the art was high at the time in genetic vector construction, and it is known that genetic vectors could be modified by replacing or removing different elements to meet the needs of particular interests.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector and methods taught by *Carrano et al* by choosing the RANTES promoter as the preferred promoter as taught by *Nelson et al* and replacing the antibiotic resistance gene with a suppressor tRNA or a small element as taught by *Eastman et al* with a reasonable expectation of success. Given the detailed knowledge of RANTES promoter as taught by *Nelson et al*, the ordinary skilled artisan would have been motivated to modify the claimed invention when regulating immune system are the subject of interest, and because using non-antibiotic selectable marker could avoid the potential problem of antibiotic resistance in humans. Further, given the levels of the skilled in the art, one could easily replace an element(s) of the vector for the interest of a particular need with a reasonable expectation of success. Although the cited references do not disclose a kit, it is well known in the art that it is a routine associated with commercial activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

It is noted that claim recitation "which directionally accepts cDNA" has not given patentable weight in determining the novelty of the invention. This is because it describes the intrinsic property of the sequence acceptance site, as long as there is a cloning site in the vector, it meets claim limitation. Further, the phrase "cDNA derived from rtPCR cloning via unique sites within an interrupted palindrome recognition sequence for a restriction endonucleases" has been interpreted as any cDNA, because

it is a product-by-process type of phrase wherein the product is determined by the chemical composition of the product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Claims 15, 16, 23, 78, 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755), *Nelson et al* (J Immunol 1993;151:2601-12), *Nelson et al* (J Immunol 1996;157:1139-48, IDS), and *Eastman et al* (US 6,103,470) as applied to claims 1-9, 15-31, 36, 37, 41-44, 60-62, 65-71, 77-92, 96-107, 110 above, and further in view of *Zurr et al* (US 5,648,235).

Claim 15, 16, 23, 78, 85 recite an optional internal ribosomal entry site in the humanized vector.

The teaching of *Carrano et al, Nelson et al,* and *Eastman et al* as described above fails to teach a multi-cloning site comprising an internal ribosomal entry site (IRES).

*Zurr et al* teach a method for production of desired proteins, uses an "on-off translation mechanism", i.e. including an IRES in the vector system (columns 3, lines 32-34). They go on to teach that such mechanism can be better exploited to obtain gene products in significant amounts and in a selective manner (column 3, lines 50-61).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carrano et al, Nelson et al,* and *Eastman et al* by simply combining a IRES in the expression vector as taught by *Zurr et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it could gain better control of

the expression of the gene of interest. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 32, 33, 38-40, and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755), *Nelson et al* (J Immunol 1993;151:2601-12), *Nelson et al* (J Immunol 1996;157:1139-48, IDS), and *Eastman et al* (US 6,103,470) as applied to claims 1-9, 15-31, 36, 37, 41-44, 60-62, 65-71, 77-92, 96-107, 110 above, and further in view of further in view of *Danko et al* (Gene Ther 1994;1:114-121).

Claims 32-33, 38-40, and 93-95 are directed to administering an expression-enhancing agent prior to administering the vector, wherein the agent is a myotoxic agent, preferably a bupivacaine-HCl.

The teachings of *Carrano et al*, *Nelson et al*, and *Eastman et al* as described above fails to teach a myotoxic agent particularly bupivacaine-HCl as an expression enhancer.

*Danko et al* teach pre-treating muscle with various myotoxic agents such as bupivacaine would enhance *in vivo* gene expression when the gene is delivered via intramuscular injection (see abstract, right column).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carrano et al*, *Nelson et al*, and *Eastman et al* by simply combining the myotoxic agent in the composition as taught by *Danko et al* with a reasonable expectation of success. The ordinary skilled artisan would

have been motivated to modify the claimed invention because the method could improve the intramuscular gene delivery. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 10, 11, 72, 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755), *Nelson et al* (J Immunol 1993;151:2601-12), *Nelson et al* (J Immunol 1996;157:1139-48, IDS), and *Eastman et al* (US 6,103,470) as applied to claims 1-9, 15-31, 36, 37, 41-44, 60-62, 65-71, 77-92, 96-107, 110 above, and further in view of further in view of *Levinson* (US 6,084,083).

Claims 10, 11, 72, and 73 are directed to a human poly-A sequence and 3' splice sequence in the vector, preferably from human growth hormone.

The teachings of *Carrano et al*, *Nelson et al*, and *Eastman et al* as described above fails to teach using a 3' untranslated region of growth hormone comprising the splice sequence and poly-A sequence.

*Levinson* supplements the teachings of *Carrano et al*, *Nelson et al*, and *Eastman et al* by disclosing that it is well known in the art before the instant effective filing date for using a 3' untranslated region of a human growth hormone comprising the splice sequence and poly-A sequence (e.g. column 91, lines 30-38).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carrano et al*, *Nelson et al*, and *Eastman et al* by simply using a 3' untranslated region of the human growth hormone in the plasmid for human gene therapy as taught by *Levinson* with a reasonable

expectation of success. Given the numerous 3' splice sequence and poly-A sequence known in the art, this limitation falls within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 12, 63, 74, 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Carrano et al* (US 6,197,755), *Nelson et al* (J Immunol 1993;151:2601-12), *Nelson et al* (J Immunol 1996;157:1139-48, IDS), and *Eastman et al* (US 6,103,470) as applied to claims 1-9, 15-31, 36, 37, 41-44, 60-62, 65-71, 77-92, 96-107, 110 above, and further in view of *Theofan et al* (US 5,674,834), and *Sloma et al* (US 5,891,701).

Claims 12, 63, 74, and 108 are directed to a specific sequence as the sequence acceptance site, i.e. SEQ ID Nos: 30 and 31.

The teachings of *Carrano et al*, *Nelson et al*, and *Eastman et al* as described above fails to teach the particular sequence sites.

However, a brief search of sequence databases would find numerous references disclosing a plasmid vector comprising SEQ ID Nos: 30 and 31. For example, US 5,674,834 discloses SEQ ID No: 30 in a plasmid vector (SEQ ID No: 8, column 7, lines 8-9), and US 5,891,701 discloses SEQ ID No: 31 in a plasmid vector (SEQ ID No: 39, column 24, line 10).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carrano et al*, *Nelson et al*, and

*Eastman et al* by simply including the synthetic sequence acceptance site as one of the candidates in vector construct with a reasonable expectation of success. Given the numerous sequence acceptance sites known in the art, this limitation falls within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 7, 10, 15-19, 23-31, 36-44, and 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Roop et al* (US 6,143,727) as applied to claims 1-3, 7, 10, 15-19, 23-31, 36-38, 41-44, 65 above, and further in view of *Danko et al* (Gene Ther 1994;1:114-121), for reasons of record and arguments addressed above under 35 USC 102 rejection.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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June 25, 2004